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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,685	06/29/2001	Rene Bruno	P23,565-A US	8546

7590 03/18/2004

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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/869,685	BRUNO, RENE	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *01 March 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-5 and 30*.

Claim(s) withdrawn from consideration: *6-29*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *Attached*

GARY NICKOL
PRIMARY EXAMINER

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit: 1642

Response to Arguments

Claims 1-5, and 30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bruno *et al.* (Cancer Surveys, Vol. 17, pages 305-313, 1993) and Urien *et al.* (Invest. New Drugs, Vol.14, pages 147-151, 1996, IDS) for the reasons of record.

Applicants reiterate that the combined references do not lend a reasonable expectation of success to the claimed method. Applicants further argue that while it is known that AAG may be the main determinant of docetaxel (taxoid) plasma binding variability and clearance, these properties, alone, fail to render obvious measuring the AAG levels in a patient to determine what dosage of a taxoid to administer to a patient. Applicants refer to Goodman and Gilman's "The Pharmacological Basis of Therapeutics" to demonstrate that other factors are involved in determining what dosage of a drug to administer to a patient, such as clearance, volume of distribution, and bioavailability. Applicants argue that each of these factors are unpredictable and can play a role in determining dosage of a given drug. This argument has been considered but is not found persuasive for the reasons of record. Further, while it is appreciated that pharmocokinetic factors such as clearance, volume of distribution, and bioavailability may be unpredictable, the teachings of Bruno *et al.* have clearly set forth a reasonable demonstration of the pharmacokinetic parameters involved with the administration of a taxoid via Phase I and II studies (page 310, Table 1) including a range of dosages, the infusion duration (hr), the peak, the area under the curve (AUC), the half-life, clearance, and excretion. Thus, in the absence of specific protein-binding information, Bruno *et al.*, alone, demonstrate reasonable guidance in the

selection of a proper taxoid dosage to be administered to a patient who is being treated for cancer.

Applicants further argue note (page 4), that "even if the Examiner persists in the belief that clearance is the sole factor relevant in the determination of a proper dose of taxoid", the state of the art at the time of applicant's invention was that it had not yet been settled as the whether AAG really was the main determinant of docetaxel clearance as claimed by Urien *et al.* Applicants note that the teachings of Marre *et al.* (Cancer Res., Vol. 56, 1996) indicated that CYP3A is a major influence on docetaxel clearance in humans. This argument has been considered but is not found persuasive. On one hand, a review of the prosecution history of this application does not appear to reveal that the Office has persisted in the belief that clearance is the sole factor relevant in the determination of a proper dose of taxoid. Secondly, with regards to the finding that CYP3A is a major influence on docetaxel clearance (Marre *et al.*), such information does not reasonably parallel the state of the art with regards to the claimed invention because it has not been shown that the metabolism and thus biotranformation of docetaxel by CYP3A would teach away or render unobvious the teachings of Urien *et al.* and Bruno *et al.* Also, with regards to Hirth *et al.* (Clincal Cancer Res, Vol. 6, 2000), applicants have argued that even after the filing date of the present application it was still uncertain whether CYP3A or AAG was the main determinant of docetaxel clearance. This argument has been considered but is not found persuasive because Hirth *et al.* admits that previous studies had larger sample sizes which may account for the observed differences of AAG's effect on clearance (1st column, page 1258). Further, Hirth *et al.* admit that docetaxel is strongly protein-bound to AAG, thus high AAG levels should decrease docetaxel clearance. Again, Hirth notes (1st column, page 1258) that

"perhaps our study did not include as many patients with AAG levels", thus providing a possible explanation for why AAG was not found to be an important predictor of docetaxel clearance in their study compared to previous findings.

Applicants further reiterate (page 5) that the disclosed references fails to teach or suggest all of the claimed limitations. This argument, having been previously considered, is not found persuasive for the reasons of record. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

GARY NICKOL
PRIMARY EXAMINER